#4

Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02000871.0

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

DEN HAAG, DEN
THE HAGUE, 27/01/03
LA HAYE, LE

Europäisches Patentamt
European Patent Office
Office européen des brevets

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 02000871.0

Anmeldetag:
Date of filing:
Date de dépôt: 15/01/02

Anmelder:
Applicant(s):
Demandeur(s):
UCB S.A.
1070 Bruxelles
BELGIUM

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Formulations containing 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
A61K9/20, A61K31/495, A61K9/28, A61K9/16, A61K9/68

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing:
Etats contractants désignés lors du depôt: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR

Bemerkungen:
Remarks:
Remarques:
SEE PAGE 1 OF THE DESCRIPTION FOR THE ORIGINAL TITLE.

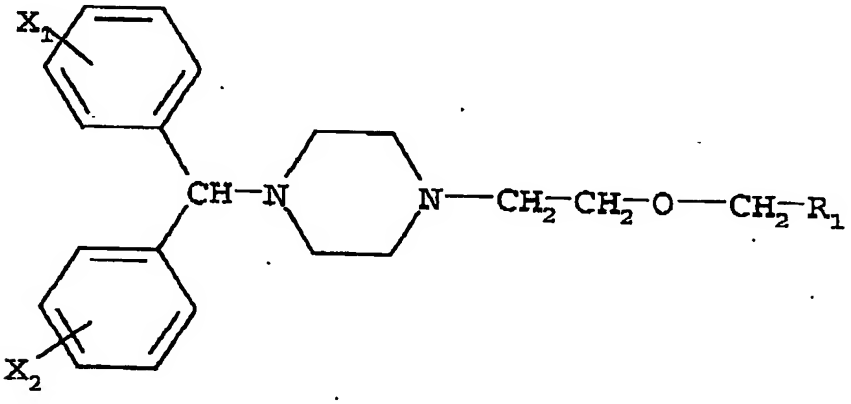
17.40.EP

Formulations

The present invention relates to pharmaceutical compositions for oral administration of active compounds.

The active compounds contemplated for use in this invention are 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids and their amides having the general formula I

Formula I



wherein

R_1 is a –COOH group or a $–CONH_2$ group, and

X_1 and X_2, taken separately, each represent a hydrogen atom, a halogen atom, a straight-chain or branched C_1-C_4 alkoxy group or a trifluoromethyl group

as well as their pharmaceutically acceptable salts, geometrical isomers, enantiomers, diastereomers and mixtures thereof.

The compounds according to formula I are orally active and selective histamine H_1-receptor antagonists. They are described in EP 0 058 146, the contents of which are incorporated herein by reference. Examples of these compounds include cetirizine, in its dihydrochloride form marketed under the tradename Zyrtec®, the (S) enantiomer thereof, levocetirizine, in its dihydrochloride form marketed under the tradename Xyzal® and efletirizine in its dihydrochloride form.

A serious problem encountered with oral formulations of these active compounds is their taste caused by the bitterness of the active compounds of formula I. This is particularly pronounced in chewable and quickly dissolving preparations.

Several attempts have been made in the prior art to mask the bitterness of active agents in general.

US 5,244,881 for example teaches that inclusion into cyclodextrin can mask the bitter taste of the active agent imipramine or its derivative trimipramine. The inclusion complex is prepared by dissolving imipramine or trimipramine and cyclodextrin in a small amount of water or solvent, carefully mixing the mixture obtained and evaporating the said mixture.

However, masking the taste is not always sufficient to obtain palatable pharmaceutical compositions. Good palatability usually further necessitates addition of polyols to the composition. The term "polyol" as used herein includes xylitol, mannitol, sorbitol, dextrose, sucrose, lactose, maltodextrins, alpha cyclodextrins, beta cyclodextrins, gamma cyclodextrins and polysaccharides, but is not limited thereto. Mannitol has proven to be a particularly suitable substance for the improvement of the palatability of preparations containing active compounds of formula I. Such compositions have, however, an important drawback. Compounds of formula I in the presence of certain polyols, including mannitol, can result in undesired reaction products such as for example those disclosed in EP 0 811 374. This side reaction is increased in presence of water and/or by an increase of temperature. The presence of mannitol and other polyols may thus create a stability problem for compounds of formula I.

Until now, to avoid undesired reaction products, there was no choice but to avoid the presence of these polyols in compositions or to coat active compounds of formula I for example with a cellulose or acrylate polymer prior to formulation.

In the first case, using other excipients like microcrystalline cellulose impairs the taste of the tablets by the fact that microcrystalline cellulose is not entirely soluble in water and therefore can leave a sand-like feeling in the mouth.

In the second case, the thickness of the coating necessary for avoiding interactions between the active compounds of formula I and the polyol(s) impedes rapid liberation of the drug from the pharmaceutical form.

It is the aim of the present invention to overcome this drawback of stability loss in the presence of polyols in a way which is both palatable and avoids disadvantageous changes in product performance.

The problem to be solved by the invention was therefore to improve the taste and palatability of oral compositions containing active compounds of formula I and polyols whilst at the same time avoiding any stability impairment and maintaining optimal release kinetics for the active compound.

The inventors have found that stability loss caused by interaction of active compounds of formula I and polyols correlates with decreasing molecular weights of the polyols.

Table 1. Molecular weights of some polyols

Polyols	MW
Xylitol	152.15
Mannitol	182.17
Sorbitol	182.17
Dextrose	198.17
Sucrose	342.30
Lactose	342.30
Maltodextrins	from 900.00
Alpha cyclodextrin	972.00
Beta cyclodextrin	1135.00
Gamma cyclodextrin	1297.00
Microcrystalline cellulose	36000

Generally, polyols with a low molecular weight, such as xylitol, mannitol, sorbitol, dextrose or sucrose (see Table 1) are reactive or very reactive and cause a large amount of undesired reaction products. On the other hand, polyols with a high molecular weight, such as cyclodextrins (see Table 1) are very little reactive.

Surprisingly, this correlation between the molecular weight and the reactivity is not true for lactose. Lactose has the same molecular weight as sucrose but shows practically no reactivity with the active compounds of formula I.

Very reactive polyols may therefore be defined as those polyols having a molecular weight of less than 300. Reactive polyols are those having a molecular weight between 300 and 950, with the exception of lactose.

It has further been found by the inventors that even reactive and very reactive polyols do not cause untolerable amounts of undesired reaction products with the active compounds of formula I if the molar ratio between these polyols and the active compound does not exceed 10. If the molar ratio between reactive or very reactive polyols and the active compound of formula I is not above 5, the percentage of undesired side products is even further minimised.

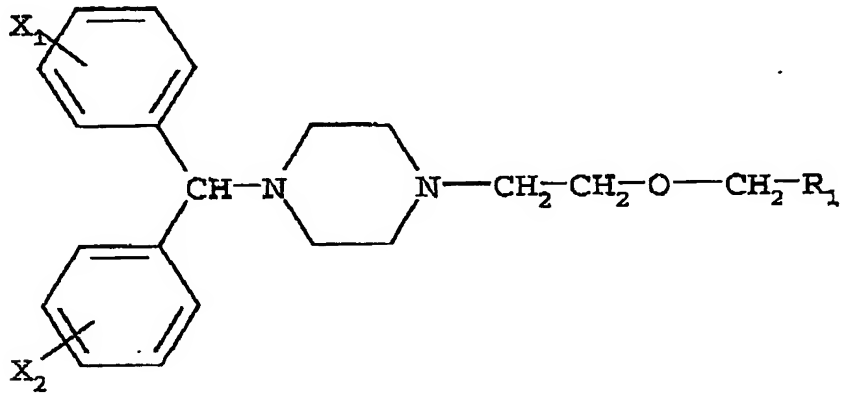
Based on these findings, the technical problem has been solved according to the present invention by providing a composition prepared from two formulations which contains in the first formulation the active compound of formula I and reactive or very

reactive polyols only up to a critical level and which contains in the second formulation the
polyols necessary to achieve a pleasant taste but no drug compound. Thereby, formation of undesired reaction products is largely eliminated and the unpleasant taste is efficiently reduced or masked.

The invention relates thus to an oral pharmaceutical composition containing at least two separate formulations:

- a first formulation, which contains an active compound selected from 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids and their amides having the general formula I

Formula I



wherein
R_1 is a –COOH group or a $–CONH_2$ group, and
X_1 and X_2, taken separately, each represent a hydrogen atom, a halogen atom, a straight chain or branched C_1-C_4 alkoxy group or a trifluoromethyl group, as well as their pharmaceutically acceptable salts, geometrical isomers, enantiomers, diastereomers and mixtures thereof, and which first formulation does not contain polyols having a molecular weight of less than 300 in a molar ratio between the polyol and active compound of formula I above 10; and

- a second formulation, which contains one or more polyol(s) and is free of any drug.

In a preferred embodiment, the first formulation does not contain polyols having a molecular weight of less than 950 in a molar ratio between polyol and active compound of formula I above 10, with the exception of lactose. Since lactose has no significant reactivity with the active compounds of formula I, it may be present in higher ratios.

In another preferred embodiment of the invention, the first formulation does not contain polyols having a molecular weight of less than 300 in a molar ratio between polyol and active compound of formula I above 5.

In a more preferred embodiment, the first formulation does not contain polyols having a molecular weight of less than 950 in a molar ratio between polyol and active compound of formula I above 5 with the exception of lactose.

In a still more preferred embodiment, the first formulation does not contain polyols having a molecular weight of less than 300.

In another still more preferred embodiment, the first formulation does not contain polyols having a molecular weight of less than 950, with the exception of lactose.

The term active compounds of formula I as used in this invention relates to 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids and their amides having the general formula I as defined above and also to non-toxic, pharmaceutically acceptable salts, geometrical isomers, enantiomers, diastereomers and mixtures thereof (racemates).

The term drug includes the active compounds of formula I as well as any other drug.

Polyols used in the second formulation are typically those which have the ability to reduce the bitter taste of the active compounds of formula I and to improve the palatability of the preparation. Examples include sorbitol, xylitol, maltitol, dextrose, sucrose, polysaccharides and preferably mannitol.

The formulations are prepared in the form of powders, granules, solutions or suspensions.

Solutions or suspensions are used to carry out a coating.

The first and/or second formulation can also contain an alcalinizing agent, preferably sodium citrate. This agent further decreases the production of undesired reaction products between polyols and active compounds of formula I.

The first formulation can contain one or more additional excipients such as colloidal anhydrous silica, microcristalline cellulose, magnesium stearate, flavors or colorants or mixtures thereof.

The first formulation may also contain polyols provided that they do not fall under the provisos of a specific molecular weight in a specific molar ratio as set out above. The first formulation can still further contain non-polyol sweetening agents such as

acesulfame K, aspartame, saccharine, saccharine sodium, cyclamate.

Flavors suitable for use in the present invention include essential oils and synthetic flavors such as citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil, oil of wintergreen, anise, eucalyptus and the like. Other artificial flavors known to those skilled in the art are also within the scope of this invention.

All forms of oral composition are envisaged by this invention, including tablets, chewing gums, effervescent tablets or dry syrup.

A dry syrup is defined as a solid formulation such as for example powder or granules destinated to be administered orally in this form or after addition to a liquid.

Accordingly, the present invention relates in a particular embodiment to bi-layer tablets wherein each of the layers is prepared from one of the formulations.

Both formulations of powders are mixed separately and then compressed in a bi-layer rotary tablet press.

The term compression is defined as the reduction in volume of a powder bed due to the application of stress (see "Pharmaceutical powder compaction technology" edited by Göran Alderborn and Chryster Nyström, p. vii, Marcel Dekker, Inc., New York).

In another embodiment, the invention relates to a three-layer tablet wherein an inert layer separates the layers prepared from the two formulations.

Further tablet designs which are also in accordance with this invention include e.g. a "sandwich" design, wherein an inner layer made from one formulation is coated on both sides by layers made from the other formulation or double tablets having an inner core prepared from one formulation and an outer shell made from the other formulation or multi-layer tablets comprising further layers in addition to a first and second layer prepared from the first and second formulation.

A further embodiment of the invention relates to a dry syrup made of a mixture of the two formulations prepared in the form of granules, one containing the active compounds of formula I and one containing the polyol(s).

In this case, the powder formulations are mixed separately and then are compacted, milled and sieved separately and two kind of granules are obtained. These granules are mixed together to give the final product.

A separate compaction of each formulation is preferred for preparing an effective dry syrup.

The term compaction is defined as the transformation of a powder into a coherent specimen of defined shape by powder compression (see "Pharmaceutical powder compaction technology" edited by Göran Alderborn and Chryster Nyström, p. vii, Marcel Dekker, Inc., New York).

A yet further embodiment of this invention relates to a chewing gum made up for instance of a core made from the first formulation and additionally containing the gum base and a coating made from the second formulation. Alternatively, the chewing gum may be made up of core made from the second formulation and additionally containing the gum base and a coating made from the first formulation.

The gum base used in the present invention for the preparation of a chewing gum may be any suitable gum base known in the art, including natural and synthetic gum bases.

All compositions according to the present invention may contain one or more additional outer coatings.

When a cyclodextrin is present, the molar ratio between cyclodextrin and the active substance of formula I ranges from 10:1 to 1:1.

The weight ratio between the first formulation and the second formulation is 1:20 to 20:1.

Another embodiment relates to a method of preparing a composition in accordance with the present invention by separately preparing the first formulation, preparing the second formulation and combining the two formulations.

The formulations are obtained by usual technologies, such as compression, direct compression, granulation, wet granulation, coating. The technologies are known by the man skilled in the art.

Further taste masking technologies can be used together with this invention. The masking properties may be obtained by applying the masking technologies to one or both formulations.

The present invention is illustrated by the following examples.

Example 1. Cetirizine bi-layer chewable tablets.

Two formulations were prepared separately. Tables 2 and 3 give the compositions of these formulations.

Table 2. Composition of the cetirizine.2HCl formulation for bi-layer tablets.

Components	Composition (mg/tablet)
Cetirizine.2HCl	10.00
ß cyclodextrin	82.50
Acesulfam K	3.50
Silica colloidal anhydrous	1.10
Microcrystalline cellulose	43.86
Flavors	0.80
Lactose monohydrate	55.00
Dyes	0.48
Magnesium stearate	2.76

Table 3. Composition of the mannitol formulation for bi-layer tablets.

Components	Composition (mg/tablet)
Mannitol	241.21
Acesulfam K	4.69
Flavors	1.00
Dyes	0.60
Magnesium stearate	2.50

Cetirizine and mannitol formulations were then compressed on a rotary bi-layer tablet press (eg Courtoy 292/43).

The tablets were placed at 25°C – 60 % relative humidity (RH), 30°C – 60 % RH and 40°C – 75 % RH during 3 months in aluminium/aluminium blisters (Alu/Alu blisters) and high density polyethylene (HDPE) bottles. Table 4 gives the results of this stability study.

Table 4. Stability study of cetirizine chewable bi-layer tablets.

Packaging	Conditions	Cetirizine (%)	Reaction products (%)
HDPE bottles	25°C – 60 % RH	100.50	0.10
	30°C – 60 % RH	100.00	0.20
	40°C – 75 % RH	99.27	0.29
Alu/Alu blisters	25°C – 60 % RH	96.28	0.10
	30°C – 60 % RH	99.32	BLQ
	40°C – 75 % RH	99.99	0.22

BLQ: below limit of quantification (= 0.1 %)

Water content, resistance to crushing, desintegration time, dissolution kinetic were also determined and all the tablets, whatever were the storage conditions, comply with all specifications.

Example 2. Cetirizine dry syrup.

Two formulations were prepared separately. Tables 5 and 6 give the compositions of these formulations.

Table 5. Compositions of the cetirizine.2HCl formulations for dry syrups.

Components	Composition (mg) A	B	C
Cetirizine.2HCl	10.00	10.00	10.00
ß cyclodextrin	82.50	82.50	82.50
Acesulfam K	3.00	3.00	3.00
Microcrystalline cellulose	279.00	83.70	0.00
Lactose monohydrate	0.00	195.30	0.00
Sodium citrate	25.50	25.50	0.00
Total	400.00	400.00	95.50

Table 6. Composition of the mannitol formulation for dry syrups.

Components	Composition (mg) D
Mannitol	399.60
Flavor	0.40
Total	400.00

The formulations A, B, C and D were compacted, milled and sieved separately and granules A', B', C' and D' were obtained. The final composition of the dry syrups were obtained by mixing the granules A', B', C' and D' according to the proportions described in table 7.

Table 7. Dry syrups compositions.

Compositions	Components (mg) A'	B'	C'	D'
E	400.00	0.00	0.00	400.00
F	0.00	400.00	0.00	400.00
G	0.00	0.00	95.50	404.50
H	100.00	0.00	0.00	200.00

The dry syrups were placed at 25°C – 60 % RH, 30°C – 60 % RH and 40°C – 75 % RH during 10 weeks in Aluminium/Aluminium blisters. Table 8 gives the percentages of undesired reaction products detected in the preparations.

Table 8. Percentages of undesired reaction products in dry syrups after 10 weeks.

Compositions	Conditions	Reaction products (%)
E	25°C – 60 % RH	0.00
	30°C – 60 % RH	0.00
	40°C – 75 % RH	0.26
F	25°C – 60 % RH	0.00
	30°C – 60 % RH	0.00
	40°C – 75 % RH	0.31
G	25°C – 60 % RH	0.00
	30°C – 60 % RH	0.06
	40°C – 75 % RH	0.34
H	25°C – 60 % RH	0.03
	30°C – 60 % RH	0.04
	40°C – 75 % RH	0.30

All the formulations comply with the specifications.

Example 3. Cetirizine chewing gum.

A composition of a chewing gum made up of a core containing cetirizine, obtained by compression, and a coating containing the polyols is given in table 9.

Table 9. Composition of the chewing gum.

Components	Composition (mg)
Core :	
Cetirizine.HCl	10.00
ß cyclodextrin	100.00
Gum base	660.00
Aspartame	3.00
Acesulfame K	2.00
Colloidal silica	30.00
Talc	30.00
Magnesium stearate	20.00
Sweetener	65.00
Flavors	80.00
Coating :	
Xylitol	382.50
Mannitol	85.00
Polyethylene glycol 6000	10.00
Titanium dioxide	10.00
Arabic gum	10.00
Flavor	2.50
Carnauba wax	0.0015

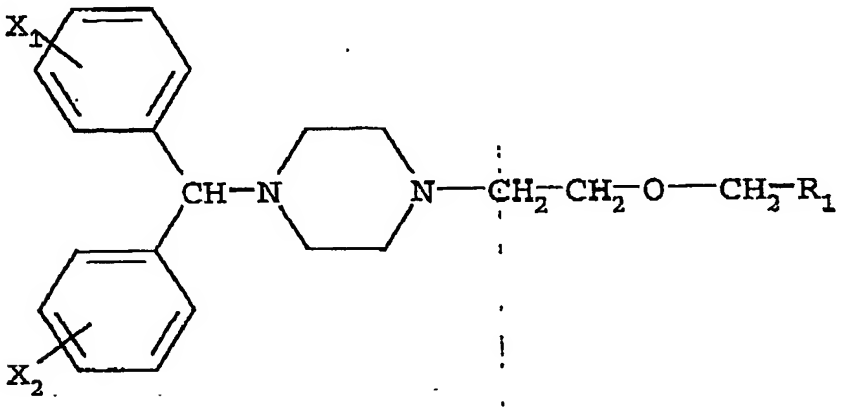
As it is the case for bilayer tablets and dry syrups, the chewing gum complies with the stability requirements.

CLAIMS

1. Oral pharmaceutical composition containing at least two separate formulations:

- a first formulation, which contains an active compound selected from 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids and their amides having the general formula I

Formula I



wherein

R_1 is a –COOH group or a $-CONH_2$ group, and

X_1 and X_2, taken separately, each represent a hydrogen atom, a halogen atom, a straight-chain or branched C_1-C_4 alkoxy group or a trifluoromethyl group as well as their pharmaceutically acceptable salts, geometrical isomers, enantiomers, diastereomers and mixtures thereof, and which first formulation does not contain polyols having a molecular weight of less than 300 in a molar ratio between the polyol and active compound of formula I above 10; and

- a second formulation, which contains one or more polyol(s) and is free of any drug.

2. A composition according to claim 1 wherein the first formulation does not contain polyols having a molecular weight of less than 950 in a molar ratio between polyol and active compound of formula I above 10, with the exception of lactose.

3. A composition according to claim 1 wherein the first formulation does not contain polyols having a molecular weight of less than 300 in a molar ratio between polyol and active compound of formula I above 5.

4. A composition according to any of claims 1-3 wherein the first formulation does not contain polyols having a molecular weight of less than 300.

5. A composition according to any of claims 1-3 wherein the first formulation does not contain polyols having a molecular weight of less than 950 in a molar ratio between polyol and active compound of formula I above 5, with the exception of lactose.

6. A composition according to any of claims 1-5 wherein the first formulation does not contain polyols having a molecular weight of less than 950, with the exception of lactose.

7. A composition according to any of claims 1-6 wherein the formulations are prepared in the form of powders, granules, solutions or suspensions.

8. A composition according to any of claims 1-7 wherein the polyol in the second formulation is mannitol.

9. A composition according to any of claims 1-7 wherein the polyol in the second formulation is a polysaccharide.

10. A composition according to any of claims 1-9 wherein at least one of the formulations further contains an alcalinizing agent.

11. A composition according to claim 10 wherein the alcalinizing agent is sodium citrate.

12. A composition according to any of claims 1-10 wherein the first formulation further contains one or more excipients selected from cyclodextrins, colloidal anhydrous silica, microcristalline cellulose, magnesium stearate, flavors or colorants.

13. A composition according to any of claims 1-12 wherein the first formulation further contains non-polyol sweetening agents such as acesulfame K, aspartame, saccharine, saccharine sodium or cyclamate.

14. A composition according to any of claims 1-13 wherein the active compound in the first formulation is cetirizine dihydrochloride, levocetirizine dihydrochloride or efletirizine dihydrochloride.

15. A composition according to any of claims 1-14 wherein it is in the form of a chewing gum, tablet or effervescent tablet.

16. A composition according to claim 15 in the form of a multi-layer tablet wherein each of the layers is prepared from one of the formulations.

17. A composition according to claim 16 in the form of a multi-layer tablet wherein an inert layer separates the layers prepared from the two formulations.

18. A composition according to claim 15 wherein it is a tablet having an inner core prepared from one of the formulation and an outer shell prepared from the other formulation.

19. A composition according to claim 15 wherein it is a chewing gum that comprises

- a core made from the first formulation and additionally containing the gum base, and
- a coating made from the second formulation.

20. A composition according to claim 15 wherein it is a chewing gum that comprises

- a core made from the second formulation and additionally containing the gum base, and

a coating made from the first formulation.

21. A composition according to any of claims 1-14 wherein it is a dry syrup prepared from a mixture of two types of granules wherein one type of granules is made by compaction of the first formulation and the other type of granules is made by compaction of the second formulation.

22. A method of preparing a composition according to any of claims 1-21 by separately preparing the first formulation, preparing the second formulation and combining the two formulations.

ABSTRACT

The present invention relates to pharmaceutical compositions for oral administration of active compounds.